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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,892	02/27/2002	Shukti Chakravarti	P-CW 4945	1524

23601 7590 03/22/2006

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EXAMINER	
LIU, SUE XU	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,892	CHAKRAVARTI, SHUKTI	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16-18 and 27-36* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note the change of examiner for the instant application.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/13/2006 has been entered.

Claim Status

2. Claims 14, 15, and 19-26 have been canceled;

Claims 27-36 have been added as new claims;

Claims 1-13, 16-18 and 27-36 are currently pending;

Claims 27-36 are being examined in this application.

Election/Restrictions

3. Applicant's election of Claims 27-36 in the reply filed on 1/13/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 1-13 and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/13/2006.

Priority

5. This application is a CIP of 09/694,758 (filed on 10/23/2000), which claims priority to provisional applications 60/160,835 (filed on 10/21/1999).

Rejections Withdrawn

6. In light of the amendments to the claims, the following rejections set forth in the previous office action are withdrawn due to the cancellation of the Claims 14, 15, and 19-26:

1.) The written description (35 U.S.C. §112, first paragraph) rejection;

2.) The 35 U.S.C. §112, second paragraph rejection;

3.) The 35 U.S.C. §102 (b) rejection;

4.) The 35 U.S.C. §103 (a) rejection;

5.) The 35 U.S.C. §102 (b)/103(a) rejection;

6.) The 35 U.S.C. §102 (b) or (e)/103(a) rejection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

8. Claims 27-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to an array comprising nucleic acid probes for determining gene expression levels of at least of the listed specific genes. The said array has the intended use of diagnosing inflammatory bowel diseases by comparing different gene expression levels.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

Written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not case involves question of priority, since requirement applies to all inventions including chemical inventions, and since the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide description of compound sufficient to distinguish

infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

The instant specification and/or the aforementioned claims do not provide adequate written description to show possession of the entire genus of IBD. IBD encompasses a variety of diseases with different symptoms and clinical manifestations as taught by, for example, Robbins et al. (Pathologic Basis of Disease. 2nd ed., 1979. Page 958 and Page 982). The instant specification and/or claims do not provide an adequate number of representing species of the different diseases. It is not clear in the instant specification or claims that the claimed probes for the different genes can be used for monitoring gene expression in all inflammatory bowel diseases. For example, a specific gene might be overexpressed compared to the control sample in one type of IBD, but may be normally expressed in another type of IBD. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The instant claims are drawn to an array comprising various nucleic acid probes, which are used to determine the gene expression level of at least one gene in a sample. The instant specification defines the term Microarray as "an array of distinct polynucleotides or oligonucleotides synthesized on a substrate..." (para. [0070]), which is interpreted to mean that the DNA microarray contains nucleic acids with defined sequences. However, neither the instant specification nor the claims specifically recite nucleic acid probes that constitute the claimed array. Claim 27 recites an array comprising nucleic acid probes for determining an expression level of at least one gene from 4 listed genes (i.e. GRO3, HNL, elafin, and COL6A3). The said "nucleic acid probes" could be different DNA molecules such as cDNA of the claimed genes, or

short oligomers that are complementary to either the coding strand or the complement strand. The probes could also contain mutations relative to the wildtype gene sequences. The probes could even be complements to genes that regulate the said 4 genes. In addition, the probes could also have various lengths or sequence segment within the claimed gene sequence. These different variables together would create almost infinite combinations of different probes that could be encompassed by the claimed array of the probes. Furthermore, the instant specification and the claims only provide GenBank accession number for the claimed genes. Furthermore, the claims and the specification only define the specific genes by their GENBANK accession numbers. The specific sequences for the probes that can hybridize to these genes are not provided. In addition, the GENBANK accession number do not provide a reference to a stable, know and non-changing source of information. GENBANK information may be updated and revised anytime (see http://www.ncbi.nih.gov/Genbank/index.html (2006) under the heading Updating or Revising a Sequence), therefore, the sequence for the claimed genes could change anytime. One skilled in the art would not be able to envision that the applicants' had possession of the recited invention as described. It is unclear as to what portion of the gene sequences are used, or suitable for the said probes for the array.

As discussed above, the skilled artisan cannot envision the nucleic acid probes that constitute the said array. Regardless of the complexity or simplicity of the method of creating such composition, adequate written description requires more than a mere statement that it is part of the invention and reference to a possibility of creating it. The composition itself is required.

Claim 30 recites the phrase "distinguishing between UC and CD", which is not clearly defined as to how the array distinguishes between the two diseases. Although the instant

specification discloses a few examples of gene over-expression in UC samples (including GRO and HNL; [0031] and [0032] of the Spec.), the disclosure does not provide specific comparison for the claimed gene expression pattern between the two diseases (UC and CD). For examples, What are the expression pattern for these genes (e.g. GRO3, HNL, COL6A3, etc.) in samples from CD subjects? How are the gene expression patterns different for these specific genes?

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 27-36 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "said subject" in line 9. There is insufficient antecedent basis for this limitation in the claim. It is not clear to which subject (healthy subject or diseased subject) the "said subject" is referring.

Claim 31 recites the phrase "the expression level of said gene product differs by at least a factor of two", which is not clearly defined. It is not clear as to from what the said gene product's expression level is to differ. Is the comparison between the recited four genes or between different subjects? The specification and the claims also do not clearly define the term ("at least by a factor of two") that used to measure the differences. For example, Does it mean that the relative amount of mRNA in the sample is two times more than the control sample? Or does it mean that the absolute mRNA amount is decreased by certain amount as compared to the control sample?

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 27-36 are rejected under **35 U.S.C. 102(e)** as being anticipated by Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998).

The instant claims are drawn to an array comprising nucleic acid probes for determining an expression level of at least one gene product in a sample from a subject. The gene product is an mRNA from at least one of the listed four genes (GRO3, HNL, elafin and COL6A3). The said array has intended use of diagnosing inflammatory bowel disease and distinguishing between UC and CD.

Cocks et al teach a microarray comprising cDNAs with SEQ ID Nos: 1-1508 (See Claim 1 of the reference). The reference teaches the cDNAs (would read on nucleic acid probes that specifically hybridize to the gene product) are immobilized on a substrate and are hybridizable elements on a microarray (Claims 2 and 3 of the reference). The reference also teaches that SEQ ID No 1100 is human cytokine (GRO-γ) (See Table 1 of the reference), which reads on GRO3. The reference further teaches that the transcripts (mRNA) used with the array are obtained from various sources such as inflamed samples and noninflamed biological samples from various tissues such as hematopoietic tissues or colon tissues (Col. 7, 1st paragraph and lines 10-25),

which would read on gene product from a sample of a subject. In addition, the reference teaches comparing the hybridization pattern from diseased and non-diseased samples (Claim 4), which would read on the intended use of the instant claim. The reference also teaches that the immunopathological condition is Crohn's disease, and/or ulcerative colitis. The reference further teaches that transcript levels are preferably at least about 2xhigher in a diseased sample than in the nondiseased sample (Col. 7, lines 22-25). Furthermore, the reference teaches that the polynucleotide probes can be synthesized on the surface of the substrate by using n covalent bonding to the substrate (Col. 10, lines 20-22, for example), and the substrates used could be chips, membrane, plates, etc. (Col. 10, lines 1-5; would read on two-dimensional matrix or array).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Dieckgraefe et al (Gastroenterology, vol. 114, no. 4, G3954; April, 1998; cited previously; IDS 8/12/2002), in view of Nielsen et al (Gut, Vol. 38: 414-420; 1996).

The instant claims are drawn to an array comprising nucleic acid probes for determining an expression level of at least one gene product in a sample from a subject. The gene product is

an mRNA from at least one of the listed four genes. The said array has intended use of diagnosing inflammatory bowel disease.

Dieckgraefe et al, throughout the publication, disclose characterization of mucosal gene expression in inflammatory bowel disease (IBD) by direct hybridization to massive parallel oligonucleotide arrays. The reference discloses that parallel or high throughput methods of measuring gene expression have been recently developed which allow concurrent measurement of the expression pattern of a large number of genes. The reference discloses the use of Gene chip (refers to the solid support chip and two dimensional matrix of the instant claims) expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohn's colitis to identify genotypes associated with particular disease. This would read on distinguishing between UC and CD. The reference discloses that RNA isolated from the mucosal colonial specimens was used to generate hybridization probes. The reference further discloses that light directed solid phase (refers to the support of the instant claims) combinatorial chemistry (would refer to covalent bonding of probes to the substrate) was used to generate oligonucleotide probe arrays (refers to nucleic acid probes of the instant claim array) which provide representation of nearly 7000 human cDNA and EST sequences, which would refer to the instant claim probes specifically hybridize to the gene products. The reference further discloses that hybridization to the oligonucleotide arrays was sensitive, specific and reproducible.

Dieckgraefe et al do not specifically teach the specific genes listed in Claim 1 of the instant application.

However, Nielsen et al teach a neutrophil gelatinase associated lipocalin that over expressed in the epithelial cells in inflammatory bowel diseases (See abstract of the reference).

The reference also teaches that the synthesis (expression) of human neutrophil lipocalin is an important cellular response to inflammation in colon epithelium, and the faecal content of the protein may therefore prove to be a useful marker for disease activity in inflammatory bowel disease (See Page 419, right col. Last paragraph). The reference also teaches (page 416, left col. 4th para.) affected tissues from ulcerative colitis and Crohn's disease showed stron NGAL expression whereas unaffected tissues were negative fro NGAL expression, which absent evidence to the contrary, read upon expression levels of gene products that differe by at least a factor of two. As a practical matter, the patent office is not equipped to manufacture products and compare them to prior art products. *In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).*

It would have been prima facie obvious at the time the invention was made for one of ordinary skilled in the art to generate an array with nucleic acid probes that specifically hybridize with a particular gene (e.g. HNL) for the purpose of diagnosing IBD.

Because Nielsen et al teach that the specific gene for the human neutrophil lipocalin could be a marker for detecting IBD, a person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for that gene.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications since the method of generating a microarray with specific nucleic acid probes are know in the art such as the one taught by Dieckgraefe et al and the specific gene sequence for the desired marker is also know as taught by Nielsen et al.

In conclusion, the invention of the instant claims would have been prima facie obvious over Dieckgraefe et al, in view of Nielsen et al to one of ordinary skill in the art without evidence to the contrary.

15. Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Dieckgraefe et al (Gastroenterology, vol. 114, no. 4, G3954), in view of Cocks et al (US 6,607,879; 2003; filed 2/9/1998).

The instant claims are drawn to an array comprising nucleic acid probes for determining an expression level of at least one gene product in a sample from a subject. The gene product is an mRNA from at least one of the listed four genes. The said array has intended use of diagnosing inflammatory bowel disease.

Dieckgraefe et al disclose characterization of mucosal gene expression in inflammatory bowel disease (IBD) by direct hybridization to massive parallel oligonucleotide arrays as describe supra.

Dieckgraefe et al do not specifically teach the specific genes listed in Claim 1 of the instant application. The reference also does not teach that the expression level of the gene product differs by at least a factor of two.

However, Cocks et al teach GRO3 gene used in an array and the gene expression difference as discussed in the above 102 (e) rejection and is herein incorporated by reference in its entirety.

It would have been prima facie obvious at the time the invention was made for one of ordinary skilled in the art to generate an array with nucleic acid probes that specifically hybridize with a particular gene (e.g. GRO3) for the purpose of diagnosing IBD.

Because Cocks et al teach that the probes for the specific gene was used in an array, a person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for that gene.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications since the method of generating a microarray with specific nucleic acid probes are know in the art such as the one taught by Dieckgraefe et al and the specific gene sequence for the desired marker is also know as taught by Cocks et al.

In conclusion, the invention of the instant claims would have been prima facie obvious over Dieckgraefe et al, in view of Cocks et al to one of ordinary skill in the art without evidence to the contrary.

16. Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Heller et al (Proc. Natl. Acad. Sci. USA. Vol. 94, pages 2150-2155, March 1997; cited previously), in view of Cocks et al (US 6,607,879; 2003; filed 2/9/1998).

The instant claims are drawn to an array comprising nucleic acid probes for determining an expression level of at least one gene product in a sample from a subject. The gene product is an mRNA from at least one of the listed four genes. The said array has intended use of diagnosing inflammatory bowel disease.

Heller et al teach discovery and analysis of inflammatory disease related genes using cDNA micro-arrays. Heller et al teach that the cDNA micro arrays were prepared by either using all known human genes of probable significance in rheumatoid arthritis (RA), using 1056 human genes from the peripheral blood lymphocyte library (i.e., see the methods in page 2150) (reads on the instant claim array). Heller et al teach RA is a cumulative effect of several factors such as

macrophages, growth factors, inflammatory cytokines, chemokines, prostaglandins, leukotrienes, matrix degrading metalloproteinases (MMPs). The reference teaches that that the differential expression of various factors in diseased RA tissue and IBD was conducted to demonstrate the utility of the micro array method to analyze complex disease by their pattern of gene expression. Heller et al disclose a 96 gene micro array design (i.e., see the results section, page 2151 and fig.1) and 1046 element array. The reference teaches that the many of the genes were common between the RA and IBD, and many genes in 1046 cDNA micro-array hybridize with probes of both RA and IBD. The reference micro-array would read on the instant claim array. And further the reference micro-array comprises probes from following genes Il-6, Il-8, GH1, Gro1, MIP, stromelysin 1. The reference teaches that the cDNA micro-array technology could provide new targets for drug development and disease therapies, and in doing so allow for improved treatment of chronic diseases.

Heller et al do not specifically teach the specific genes listed in Claim 1 of the instant application. The reference also does not teach that the expression level of the gene product differs by at least a factor of two.

However, Cocks et al teach GRO3 gene used in an array and the gene expression difference as discussed supra.

It would have been prima facie obvious at the time the invention was made to one ordinary skilled in the art to generate an array with nucleic acid probes that specifically hybridize with a particular gene (e.g. GRO3) for the purpose of diagnosing IBD.

Because Cocks et al teach that the probes for the specific gene was used in an array, a person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for that gene.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications since the method of generating a microarray with specific nucleic acid probes are know in the art such as the one taught by Heller et al and the specific gene sequence for the desired marker is also know as taught by Cocks et al.

In conclusion, the invention of the instant claims would have been prima facie obvious over Heller et al, in view of Cocks et al to one of ordinary skill in the art without evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1639
3/8/2006

MARK SHIBUYA, PH.D.
PATENT EXAMINER